

CLAIMS

1. The combination of a growth hormone secretagogue and a p38 kinase inhibitor for use in treatment or prevention of a disease associated with deposition of A β in the brain.

2. The use, for the manufacture of a medicament for treatment or prevention of a disease associated with deposition of A β in the brain, of a growth hormone secretagogue and a p38 kinase inhibitor.

3. Use according to claim 2 wherein the disease is Alzheimer's disease.

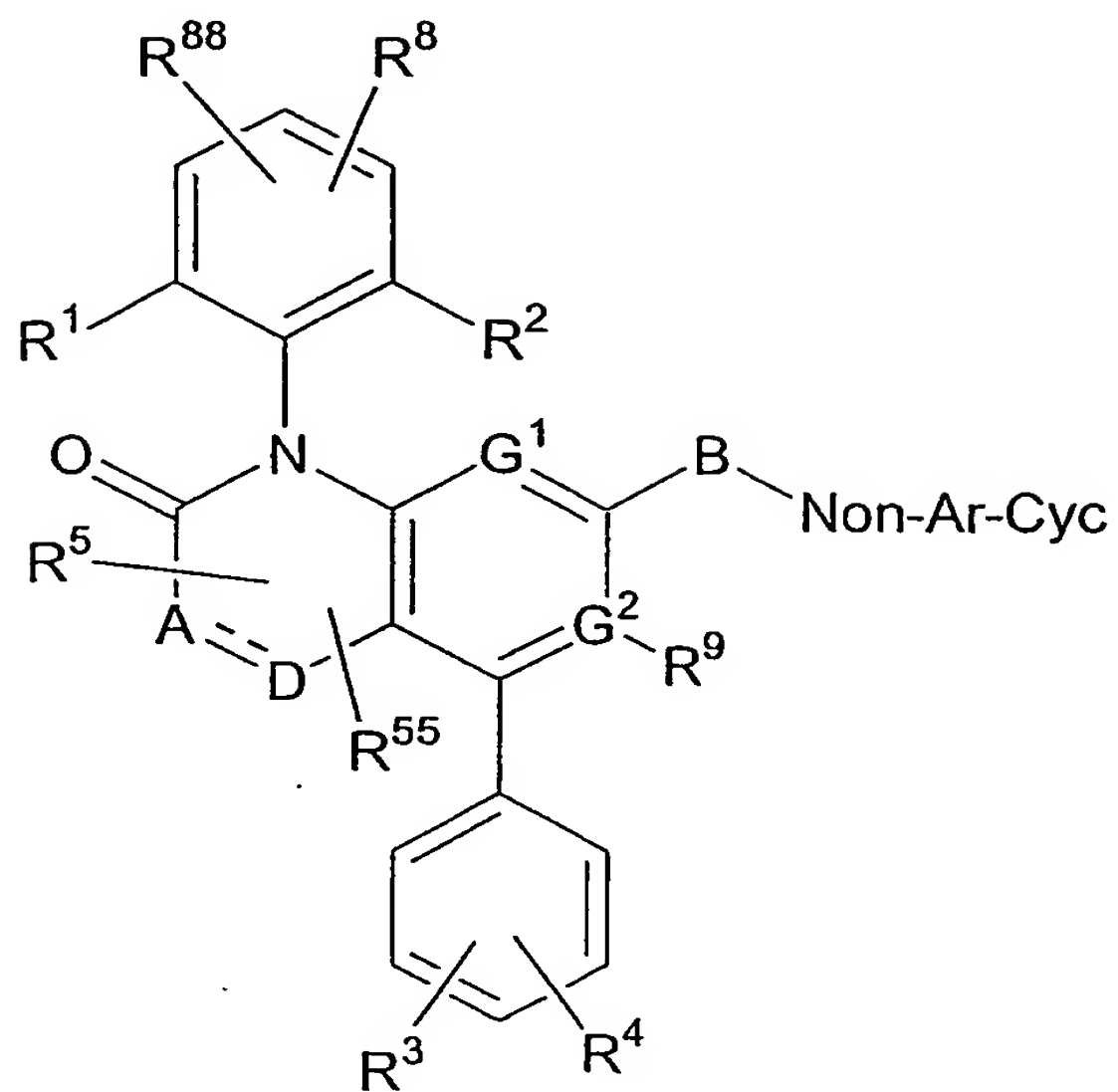
4. Use according to claim 3 wherein the medicament is for administration to a patient suffering from MCI.

5. Use according to claim 4 wherein the patient additionally possesses one or more risk factors for developing AD selected from: a family history of the disease; a genetic predisposition to the disease; elevated serum cholesterol; adult-onset diabetes mellitus; elevated baseline hippocampal volume; elevated CSF levels of total tau; elevated CSF levels of phospho-tau; and lowered CSF levels of A β (1-42).

6. Use according to any of claims 2-5 wherein the growth hormone secretagogue is N-[1(R)-[(1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethoxy)ethyl]-2-amino-2-methylpropanamide, or pharmaceutically acceptable salt thereof.

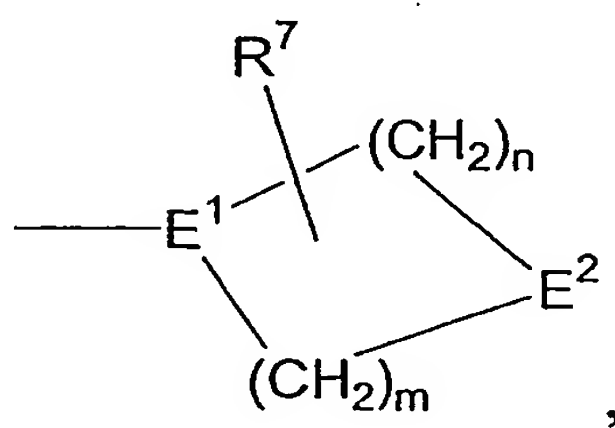
7. Use according to any of claims 2-6 wherein the p38 kinase inhibitor is a compound of formula XI:

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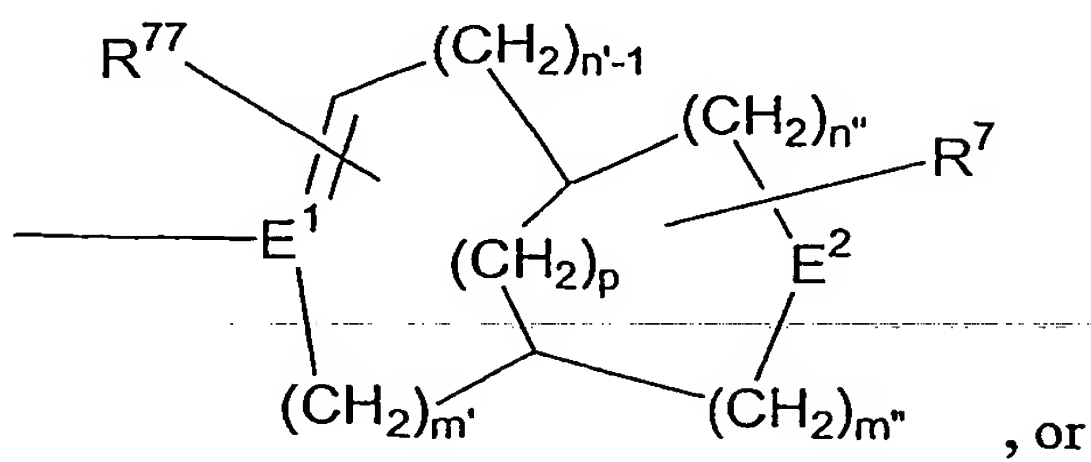
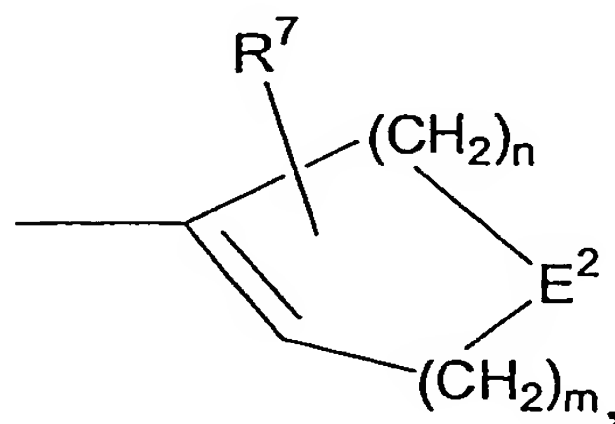


(XI)

or pharmaceutically acceptable salts thereof, wherein
Non-Ar-Cyc is

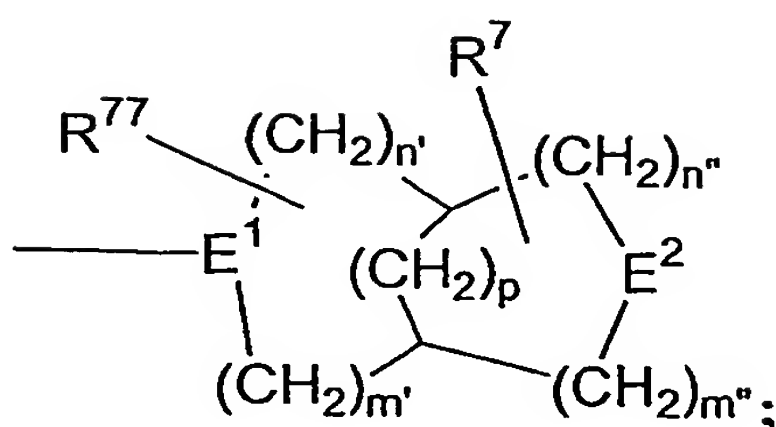


5



, or

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A is N, O, NH, CH₂, or CH;

B is -C₁₋₆alkyl-, -C₀₋₃alkyl-O-C₀₋₃alkyl-, -C₀₋₃alkyl-NH-C₀₋₃alkyl-, -C₀₋₃alkyl-NH-C₃₋₇cycloalkyl-, -C₀₋₃alkyl-N(C₀₋₃alkyl)-C(O)-C₀₋₃alkyl-, -C₀₋₃alkyl-NH-SO₂-C₀₋₃alkyl-, -C₀₋₃alkyl-, -C₀₋₃alkyl-S-C₀₋₃alkyl-, -C₀₋₃alkyl-SO₂-C₀₋₃alkyl-, -C₀₋₃alkyl-PH-C₀₋₃alkyl-, -C₀₋₃alkyl-C(O)-C₀₋₃alkyl, or a direct bond;

D is CH, CH₂, N, or NH; optionally A and D are bridged by -C₁₋₄alkyl- to form a fused bicyclo ring with A and D at the bicyclo cusps;

E¹ is CH, N, or CR⁶; or B and E¹ form -CH=C<;

E² is CH₂, CHR, C(OH)R, NH, NR, O, S, -S(O)-, or -S(O)₂-;

G¹ is N, CH, or C(C₁₋₃alkyl);

G² is N, CH, or C(C₁₋₃alkyl);

R, R⁷ and R⁷⁷ each independently is hydrogen, C₁₋₆alkyl- group, C₂₋₆alkenyl- group, C₄₋₆cycloalkyl-C₀₋₆alkyl- group, N(C₀₋₄alkyl)(C₀₋₄alkyl)-C₁₋₄alkyl-N(C₀₋₄alkyl)- group, -N(C₀₋₄alkyl)(C₀₋₄alkyl) group, C₁₋₃alkyl-CO-C₀₋₄alkyl- group, C₀₋₆alkyl-O-C(O)-C₀₋₄alkyl- group, C₀₋₆alkyl-C(O)-O-C₀₋₄alkyl- group, N(C₀₋₄alkyl)(C₀₋₄alkyl)-(C₀₋₄alkyl)C(O)(C₀₋₄alkyl)- group, phenyl-C₀₋₄alkyl- group, pyridyl-C₀₋₄alkyl- group, pyrimidinyl-C₀₋₄alkyl- group, pyrazinyl-C₀₋₄alkyl- group, thiophenyl-C₀₋₄alkyl- group, pyrazolyl-C₀₋₄alkyl- group, imidazolyl-C₀₋₄alkyl- group, triazolyl-C₀₋₄alkyl- group, azetidyl-C₀₋₄alkyl- group, pyrrolidinyl-C₀₋₄alkyl- group, isoquinolinyl-C₀₋₄alkyl- group, indanyl-C₀₋₄alkyl- group, benzothiazolyl-C₀₋₄alkyl- group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being -OH, -N(C₀₋₄alkyl)(C₀₋₄alkyl), C₁₋₄alkyl, C₁₋₆alkoxyl, C₁₋₆alkyl-CO-C₀₋₄alkyl-, pyrrolidinyl-C₀₋₄alkyl-, or halogen;

or R⁷ together with a bond from an absent ring hydrogen is =O;

n' + n'' = n;

m' + m'' = m;

n is 1, 2, 3, or 4;

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m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

5 R¹, R², R³, R⁴, and R⁶ are each independently halogen, C₀₋₄alkyl, —C(O)-O(C₀₋₄alkyl), or —C(O)-N(C₀₋₄alkyl)(C₀₋₄alkyl);

R⁵ and R⁵⁵ independently is H, CH₃, CH₂CH₃, or absent;

R⁸⁸ and R⁸ each is independently —CN, —C₀₋₄alkyl, —C(O)-N(C₀₋₄alkyl)(C₀₋₄alkyl), —C(O)-O-C₀₋₄alkyl or 1,3-dioxolan-2-yl-C₀₋₄alkyl—;

R⁹ is —C₀₋₄alkyl, or absent; and

10 any alkyl is optionally substituted with 1-6 independent halogen or —OH.

8. A pharmaceutical composition comprising in a pharmaceutically acceptable carrier, a growth hormone secretagogue and a p38 kinase inhibitor.

15 9. A kit comprising a first medicament comprising a growth hormone secretagogue and a second medicament comprising a p38 kinase inhibitor together with instructions for administering said medicaments sequentially or simultaneously to a patient suffering from AD, age-related cognitive decline, MCI, cerebral amyloid
20 angiopathy, multi-infarct dementia, dementia pugilistica or Down syndrome.

10. A method of treatment or prevention of a disease associated with deposition of A β in the brain comprising administering to a subject in need thereof a therapeutically effective amount of a growth hormone secretagogue (GHS) in
25 combination with a therapeutically effective amount of a p38 kinase inhibitor.